DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard
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Mr. Lawrence J. Goffney
Deputy Assistant Secretary of Commerce and
Deputy Commissioner of Patents and Trademarks

Dear Mr. Goffney:

This communication follows our telephone conversation of February 17, 1997 confirming your comments on expressed sequence tag (EST) patenting at the February 14th AAAS meeting in Seattle. We spoke at length of our mutual concerns that patent claims issuing on partial cDNA ESTs be commensurate in scope with their enabling disclosures. At the conclusion of our conversation, you kindly invited continued dialog with appropriate Group 1800 staff to advance this common goal. While there has been no communication back to me from Group 1800, debate on this issue continues to ferment within the biotechnology community at the National Institutes of Health (NIH), academic institutions, and industry. Therefore, I submit these written comments, herein, for consideration by you and your managers within the Biotechnology Group in anticipation that this formally initiates dialog between our offices on these matters of common interest.

Background – NIH Involvement in ESTs:

As you undoubtedly know, EST technology originated in the NIH laboratory of Dr. Craig Venter at the National Institute of Neurological Diseases and Stroke (NINDS), and we believe the first patent applications in this field were filed on Dr. Venter's discoveries by NIH in June 1991. A serious concern, at the time, was that public disclosure of EST sequences could create a prior art effect against subsequent patenting of newly discovered complete gene sequences possessing important diagnostic or therapeutic utilities. EST patent applications were filed, in significant measure, to provide short term insurance against such potential prior art blockage of future gene discoveries.

Contemporaneous with our invention filings, and continuing through the period of patent examination, the Court of Appeals for the Federal Circuit (CAFC) rendered a series of opinions drawn to DNA/protein sequences, including *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed.Cir.1991); Fiers v. Sugano, 25 USPQ2d 1601 (Fed.Cir.1993); In re Bell, 26 USPQ2d 1529 (Fed.Cir.1993);* and subsequently, *In re Deuel, 34 USPQ2d 1210 (Fed.Cir.1995)* which reduced significantly our prior art concerns. These court decisions, in conjunction with the evolution of our definitive Patent Policy that moves away from patenting research tools, led to the NIH abandoning all pending EST applications. However, the NIH continues to actively pursue varied aspects of genomic research, including transferring the useful products of that endeavor to the private sector. Despite having no EST applications pending before your office, the NIH maintains an ongoing policy interest in these compositions as long as EST technologies potentially influence the development and availability of genomic inventions for the public health.

NIH Issues and Concerns:

Like many in the biotechnology research and intellectual property communities, the NIH is both surprised and disappointed by media reports indicating the USPTO now finds the use of ESTs as probes to be a specific utility in satisfaction of Section 101 requirements. Typically, the identity of the gene corresponding to an EST is not known. NIH scientists, as well as many in the academic community (i.e., those of ordinary skill in this art), view such bare EST sequence disclosures as providing little or no practical (real world) value toward advancing discovery in the human genome art. Potential value for EST sequences derives from future research relating EST sequences to genes or proteins of known function. At best, therefore, ESTs represent a poor research tool.

The relative merit of these discoveries as research tools should not militate against their public disclosure in any forum, including scientific literature, databases, or patents. The nature of such disclosures follows from the formats, policies, and statutes governing or established by each forum. We appreciate the unique character of the patent forum that balances the value of public disclosure against the right to exclude others from the claimed invention for a limited period of time. We appreciate also the mission of the USPTO to administer the patent statutes and rules to establish in each patent grant the appropriate *quid pro quo* between public disclosure and rights of exclusivity; thereby, advancing the constitutional mandate to promote the progress of science and the useful arts.

The interest of the NIH is to provide the PTO sufficient information to make appropriate and consistent decisions in establishing this *quid pro quo* relative to EST inventions. In this regard, NIH has concerns along two lines. First, we believe the utility of the typical EST invention may not meet the threshold criteria of utility set forth in 35 USC 101. Our second concern is more critical. If EST inventions do satisfy the specific utility requirements of patent law, we are concerned the PTO understands all the relevant issues to establish an appropriate balance between the value of EST disclosures and the scope of exclusionary claim protection. In other words, we are concerned how the PTO applies the enablement and description provisions of 35 USC 112 to establish a proper claim breadth for EST inventions.

As indicated previously, the NIH no longer has a proprietary position in patenting ESTs. Therefore, the NIH, similar to the PTO, has no interest in the commercial success or failure of any particular applicant or company in this arena. Rather, the NIH communicates our concerns in this regard, because we are sensitive to the possibility that prototypical ESTs with claim scope broad enough to encompass the corresponding complete gene sequence may unduly shift the intended *quid pro quo* in favor of the patentee. The systematic promulgation of this imbalance may have serious chilling consequences to further research and commercial development of diagnostic and therapeutic products related to human genomics. Clearly, this situation could negatively affect the public health, and the advancement of the public health is the mandate of this agency.

Our primary interest, in this regard, is that a new specie of "submarine" patents not be spawn by unduly broad patents routinely issued in the EST art. This may arise through the congruence of two conditions. The first involves the expectation in the art that the PTO will issue EST patents routinely, wherein the utility of the corresponding gene is not known; yet claim scope is broad enough to encompass the entire gene. The second condition may develop as a consequence of the new sequence restriction practice, whereby up to ten nucleic or amino acid sequences may be

examined per application. The remaining sequences are withdrawn from consideration pending filing of a Divisional application. The net effect of this restriction process may be millions of confidential EST sequences lying in "limbo" within the PTO.

Upon subsequent and independent discovery of the complete gene, possessing a clinically and/or commercially significant utility, applicant resurrects the corresponding withdrawn EST species. The patent issuing on that Divisional potentially could block or retard development of the significant public health invention. The economics of this situation may be resolved within the marketplace for individual cases, and this should not be the preoccupation of the PTO; or the NIH. However, a health care issue is created if industry delays or refrains from investing in this important endeavor because of uncertainty associated with the existence of submarine ESTs lurking within the PTO. This should be a concern not only to the NIH mandate, but also to the mandate of the PTO.

Patent procedures should not encourage submarine patents that undermine the pursuit of invention. In particular, submarine ESTs portray a singularly unsatisfactory perception of a secret disclosure of *de minimis* utility, whose only real function is to lay in predatory wait and feed off later developed inventions with significant health care utility. While it may fall within the four corners of legal patent prosecution procedure, this scenario does not advance the progress of science and the useful arts. The means by which the PTO can affect this process is to circumvent the perception that useless parasitic inventions are hibernating in the Central Files of the PTO. The public must feel confident the PTO will issue patents only for inventions with claims commensurate in scope with their specific "real world" utilities.

We believe the PTO can foster this public confidence by practicing consistently the guidelines regarding Section 101 and 112 issues it has already promulgated. What follows is intended to be the constructive input of a sister government agency with a common interest in advancing the progress of science and useful public health arts.

Legal Considerations regarding the Patenting of ESTs

I. The PTO should re-evaluate whether an asserted utility as a probe represents a "specific utility" for ESTs under 35 USC 101.

It is generally accepted that there is no practical utility in the use of a probe as an intermediate to analyze or make a final product gene of unknown function (utility). Indeed, most practitioners in this art believed the issue was resolved with release of the USPTO Utility Guidelines, along with its Legal Analysis Supporting Utility Examination Guidelines, and supporting documentation available through the USPTO Home Page.

One such supporting document, titled: "Synopsis of Application of Utility Guidelines With Examples" defines "Specific utility" in part as follows:

> -a practical utility which defines a "real world" context of use.
> Utilities which require or constitute carrying out further research

> to identify or reasonably confirm a "real world" context of use are not "specific utilities".

In the instant case, the context of use as a probe has no "real world" meaning until the gene for which the EST is a probe is identified; i.e., functionally characterized. A gene with no associated biological function has no "real world" meaning. Consequently, there can be no "specific utility" in probing a gene of unknown biological function. It requires further research to ascribe a biological function to an unknown gene probed by an EST in order to provide "real world" context. This deficiency in EST inventions follows from the fundamental Supreme Court ruling in *Brenner v. Manson, 383 U.S. 519, 148 USPQ 689* that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." This theme was advanced also by the Federal Circuit in *In re Brana*, 34 USPQ2d 1436 (Fed.Cir.1995). Most recently, the Court of Appeals for the Federal Circuit in *Genentech v. Novo Nordisk, Case 96-1440, decided March 13, 1997*, invalidated a Genentech patent on cleavable fusion stating, "Genentech is attempting to bootstrap a vague statement of a problem into an enabling disclosure sufficient to dominate someone else's solution of the problem. This it cannot do."

The above indicated definition continues on to recite examples illustrating "specific utility", as well as examples illustrating the lack of "specific utility" resulting from a need for further research to identify or reasonably confirm a "real world" context of use. The instant EST scenario is consistent with three of the examples illustrating situations that do not define "specific utilities." One such example is "a method of assaying for or identifying a material that itself has no 'specific utility'". This is consistent with using an EST as a probe to assay or identify a gene that itself has no specific utility, because the gene has no known biological function. The second example is "a method of making a material that itself has no 'specific utility'". This is consistent with using an EST as a probe to make a gene that is itself has no specific utility, because the gene has no known biological function. The last example is most cogent and defines "a claim to an intermediate product for use in making a final product that has no known utility". Indeed, an EST probe for an unknown gene may be considered an intermediate for use in making a final product. In this case, the final product (i.e., the unknown gene) is a product with no known utility.

The last example regarding failure of the intermediate product to establish a "specific utility" is in concert with the probative case law. See *In re Joly, 153 USPQ 45 (CCPA 1967)* wherein Judge Rich instructs

> *** the conclusion is inescapable that, just as the practical utility of the compound produced by a chemical process "is an essential element" in establishing patentability of the process, [Brenner v. Manson] 383 U.S. 519, 148 USPQ 689, so the practical utility of the compound, or compounds, produced from a chemical "intermediate," the "starting material" in such a process, is an essential element in establishing patentability of that intermediate. It seems clear that, if a process of producing a product of only conjectural use is not itself "useful", within Section 101, it cannot be said that the starting materials for such a process—i.e., the presently claimed intermediates—are "useful.' It is not enough that the specification disclose that the intermediate exists and that it "works," reacts, or can be used to produce some intended product of no known use. Nor is it enough that the product disclosed to be

> obtained from the intermediate belongs to some class of compounds which now is, or in the future might be, the subject of research to determine some specific use.***
>
> We conclude that appellants have not discharged their burden to show that the claimed subject matter is "useful" within the requirements of Section 101

Finally, following the "Synopsis of Application of Utility Guidelines" are a set of 12 examples of common biotechnology invention scenarios designed to walk the examiner/reader through the disclosure fact pattern, claims, and analysis of relevant utility issues. Example 9 is particularly applicable in being drawn to a disclosure and claims to a large number of cDNA fragments (ESTs). The disclosed utility of each EST is as a probe to obtain the corresponding full length gene. The full length gene is used prophetically to make the corresponding protein via routine recombinant methodologies. The protein product then is used to study cellular mechanisms and activities associated with the protein. Each EST is claimed individually using closed ("consisting of") language, wherein the claim is limited to the exact disclosed Sequence ID Number. The asserted utility for each EST is identified as a method of making the corresponding protein. The example goes on to explain that the probative determination of "specific utility" is whether or not the protein product has a "specific utility". Since the asserted utility for the protein was a research utility (not a "real world" or "specific utility under Brenner v. Manson criteria), the method of making that protein (the asserted utility of the claimed EST) necessarily could not define a "real world" context of use. The conclusion reached from the analysis was that no utility existed under 35 USC 101, and both Section 101 and Section 112, 1st paragraph enablement rejections are proper.

Therefore, the standard for "specific utility" of EST-probe intermediates is the objective factual determination whether the final gene or protein products themselves possess "real world" utility (i.e., known and defined biological function). Considerations regarding advances in the state of the art, the routine nature of hybridization and recombinant DNA techniques, or the relative efficiency of the probe-intermediate for its intended purpose are of little moment in this determination. Deviation from or failure to meet this standard leads invariably to a conclusion of no "specific utility" under 35 USC 101.

NIH is not aware of any legislation or court decisions that negate or modify these reasoned guidelines recently developed by the PTO to analyze issues regarding "specific utility". It appears that a consistent application of those guidelines leads to the conclusion that EST probes have no "specific utility" under Section 101 if the corresponding gene is unknown or has no "specific utility."

II <u>If Deemed to Have Utility, The Scope of EST Claims Should Be Limited To The Specific EST Sequence.</u>

It is well established that a deficiency under Section 101 creates also a deficiency under Section 112, first paragraph, since the specification cannot enable one skilled in the art to use an invention that is not useful. *Nelson v. Bowler, 206 USPQ 881 (CCPA 1980).* Therefore, ESTs failing the above "specific utility" test as probes to unknown genes should be considered not patentable also

under the enablement provision of 35 USC 112. In the event the PTO deems any or all ESTs satisfy the utility requirements for patentability, the following arguments are set forth regarding breadth of claim scope.

A. General Considerations Regarding Scope of Claims

While monitoring polynucleotide composition claims issued recently, we observe regularly that polynucleotide claims are broader than the disclosed Sequence ID Number listings. NIH observed open "comprising" language in conjunction with claim constructions, as well as the following forms of structural (sequence) variability: allelic variants; a polynucleotide complementary to a polynucleotide in a Markush group; and less than 100% sequence identity expressed as --at least "X" % (e.g., 95%) identity to a Markush group of polynucleotides.. It is not our intent to question the propriety of claim breadth in the particular fact situations of those issued patents. However, NIH has serious concerns if EST claims will issue with similar broad open-ended claim constructions. For the reasons developed in the sections to follow, we submit it should be a rare disclosure that supports EST claim scope broader than the specific Sequence ID Number.

B. PTO Guidelines/Training Materials for Examining Patent Applications With Respect to 35 USC Section 112, First Paragraph-Enablement Chemical/ Biotechnical Applications support the proposition that ESTs should be limited in scope.

On November 5, 1996, training material and guidelines analogous to the utility guidelines were made available to the public on the PTO Home Page. Included in the materials are two examples (Examples A & B) presenting related fact patterns and claims drawn to hybridization probes and methods of using same. Claims in the first example recite open "comprising" language and Markush groups containing specific Sequence ID numbers corresponding to three disclosed nucleotide probe sequences, ranging between 30 and 35 nucleotides in length, which hybridize specifically to a defined target of known utility. The second example differs by eliminating the functional limitation drawn to the specificity of hybridization. Both examples cite a pair of literature references, Sambrook et al. and Wallace et al., for their teaching that mismatches within an oligonucleotide probe impart unpredictability to the hybridization process.

In the analysis, both examples explain how the "comprising" language markedly broadens the scope of the probe embodiment by introducing random sequences of indeterminate length. In view of the teachings of Sambrook et al. and Wallace et al. regarding the effect of base mismatching on probe specificity, the introduction of random base sequences into a hybridization probe would require undue experimentation to identify or make all nucleic acid probes encompassed by and satisfying the functional (specificity) requirements of the claim. Therefore, hybridization-probe claims containing such open-ended "comprising" language would be subject to rejection under 35 USC 112, 1st paragraph. Both examples instruct replacing the open-ended "comprising" language with "consisting" language directed specifically to the disclosed probes in order to eliminate the undue breadth problem.

The second example indicates the need for functional claim limitations directed to the specificity and utility of the probe. The lack of such functional limitations exacerbates the Section 112, 1st paragraph deficiencies associated with "comprising" language by introducing additional enablement issues drawn to failure to teach how to use all the probes encompassed by the claim.

C. Application of Enablement Guidelines to EST Inventions

The hybridization-probe examples in the PTO Enablement Guidelines relate to EST cases asserting a probe utility. EST sequences, corresponding to unknown genes or genes of unknown function (specific utility), relate to at least Example 2, above. Regardless the breadth of claim language, we submit this scenario fails the "how to use" considerations of enablement under Section 112, 1st paragraph by teaching the use of an EST moiety to probe specifically for an unknown structure. If a probe does not bind specifically, how can it be distinguished from other probes? If the EST does bind something, the person skilled in the art would not know if the probe bound the intended species. It is left to experimentation outside the teachings of the specification to define all the parameters of a successful hybridization and, thereby, the real use of the claimed probe. It is not routine in this art to require the user to discover new genes in order to use a patented hybridization probe. At the very least, this would fall into the category of requiring undue experimentation.

EST sequences related to genes of known function are not subject to the "specific utility" criticisms described previously, but do correspond to the scenario outlined in the first hybridization example, above. Consequently, EST product and method of use claims with closed "consisting of" language drawn to specific Sequence ID Numbers should be free of Section 112 enablement criticisms, assuming an adequate written disclosure setting forth how to make and use the invention, including the best mode. Introducing open "comprising" claim language, of course, would trigger the above indicated "Undue Breadth" rejection under Section 112, 1st paragraph. The introduction of more moderate claim broadening language, however, such as allelic variants, fragments thereof, having at least 90% identity, a polynucleotide complementary to, etc., should be analyzed for undue breadth on a claim by claim basis using standard *Ex parte Forman / In re Wands* considerations viewed from the perspectives elucidated in Example 1, above.

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An additional factor to be considered when ESTs are used to probe genomic DNA is that peptide coding regions (exons) generally are interrupted by non-coding introns. EST probes, derived from cDNA, reflect only exon and regulatory sequences from the genomic polynucleotide population. Consequently, the nucleotide sequence of EST probes may not be contiguous with the corresponding genomic DNA. Indeed, an EST sequence may have homology to several discontinuous regions of genomic DNA separated by multiple exons. Under such circumstances, only a variable fraction of each EST sequence probe would actually hybridize to the gene. Depending on a number of factors, including the size of the EST, introducing variability into such EST structure via claim broadening language may compromise the ability of the EST to function as a probe in concert with the considerations set forth in the Sambrook et al. and Wallace et al. citations discussed in Example 1, above. It would be expected, therefore, that any claim broadening language would be supported by appropriate working examples addressing these issues. In this regard, information gained from one EST species does carry over to different EST species. This should necessitate different working examples for each claimed EST species.

D. Additional Considerations

As indicated previously, "comprising" claim language encompasses additional random DNA sequences different from those specifically disclosed in the application. Applicants cannot describe or envisage the structure of these additional sequences. Consequently, the specification must be defective under the "description" requirement of Section 112, 1st paragraph. This interpretation is in concert with a line of Federal Circuit Decisions involving nucleic acid and amino acid structures. See *Fiers v. Sugano, 25 USPQ2d 1601 (Fed.Cir.1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed.Cir.1991)*. Also see *In re Bell, 26 USPQ2d 1529 (Fed.Cir.1993)* and *In re Deuel, 34 USPQ2d 1210 (Fed.Cir.1995)* regarding related issues drawn to treating nucleic acids as chemical structures. Furthermore, the Examiner cannot search the prior art to determine novelty and unobviousness without knowledge of which sequences are being claimed. A claim that does not define the invention with sufficient distinctness to permit a proper search of the prior art is invalid also under the second paragraph of 35 USC 112.

In summary, the NIH believes EST sequences for use as probes do not satisfy the utility requirements under Section 101 unless the EST sequences correspond to genes of known function. Furthermore, the scope of all EST probe claims should be limited to "consisting of" language consistent with the PTO guidelines for enablement issues. Indeed, we caution against any broadening of the scope of EST claims beyond the disclosed Sequence ID Number. We feel a consequence of issuing broad claims to EST sequences as probes to unknown genes could be the emergence of "submarine" patents having a chilling effect on development of genomic products for the public health. The solution to this potential health care problem merely requires the PTO to strictly and consistently adhere to existing utility and enablement examination guidelines established during the last two years.

I appreciate this opportunity to present the views of the NIH. I again hope this communication initiates ongoing dialog between our offices to advance these issues. Please feel free to contact me if I can be of any assistance.

Sincerely Yours,

/s/

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